A4 cont.

Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
GDO	200
Propylene Glycol	100
Lecithin	20
Na Deoxycholate	0.5
Glycerine	2.4
Methyl paraben	1.8
Propyl paraben	0.2
Water	q.s.

and a composition comprising:

Component	Weight (mg)
Compound of Formula 1 as defined in Claim 1	60
MCT/GDO (8:2)	200
Lecithin	20
BHT	0.1
Glycerine	2.4
Water	q.s.

REMARKS

The undersigned on behalf of applicants, would like to express appreciation to the Examiner for granting the telephonic interview on November 13, 2001. The interview was helpful in clarifying the Examiners observations concerning applicant's obligation to fulfill the requirement of 37 CFR §1.98.

It was apparent during the interview that the Examiner had not received all of the prior art information submitted by applicants. On June 12, 2000, applicants submitted an Information Disclosure Statement (IDS) under 37 CFR §§ 1.97 and 1.98, which included a Form PL-1449. A copy of this IDS is attached to this Response as Exhibit A.

On January 8, 2001, applicants submitted a Supplemental IDS under 37 CFR 1.97 and 1.98, which is attached to this

Response as Exhibit B. While the IDS did not include a Form PL-1449, it did include a copy of the International Search Report. A PL-1449 listing the documents in the International Search Report is attached to and made a part of Exhibit B.

During the interview the Examiner questioned the listing of documents under the heading Information Disclosure on page 2 of the specification. In this regard, it should be noted that the information contained under that heading is merely a concise explanation of the relevance of references listed in the PL-1449 filed June 12, 2000.

Claims 1-23 are in the application.

Claims 1-21 stand rejected under 35 USC §103(a) as being unpatentable over Romines, et al (USPN 5 852 195) and Suzuki, et al (USPN 5 693 337).

THE REJECTION OF CLAIMS 1-21 UNDER 35 USC §103(A)
AS BEING UNPATENTABLE OVER
U. S. PATENT NO. 5 852 195 and
U. S. PATENT NO. 5 693 337

This rejection is traversed because Claims 1-21 as well as new claims 22-24 are patentably distinguishable over U. S. Patent No. 5 852 195 (the 195' patent) and U. S. Patent No. 5 693 337 (the 337' patent) for the following reasons:

Present Claim 1 defines a submicron lipid emulsion pharmaceutical composition comprising (a) a therapeutically effective amount of a pyranone compound having the Formula I, (b) an oil component selected from the group consisting of mono-, di-, tri-glyceride or a mixture thereof wherein the monoglyceride and diglyceride are mono- and di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon atom chain length, wherein triglyceride is a saturated fatty acid ester of glycerol having six to twelve carbon atom chain length, (c) an emulsifying agent consisting of lecithin, and (d) a liquid phase comprising one or more pharmaceutically acceptable solvents. Support for the recitation "submicron lipid emulsion" can be found on page 7, line 13. Therefore it does not constitute new matter.

While the 195' patent discloses the compound of Formula I, it does not disclose the incorporation of Formula I into an emulsion. Furthermore, it does not disclose or suggest the incorporation of the compound of Formula I into a submicron emulsion will improve the oral biovailability of the compound over that of a simple aqueous suspension of the compound. The increased oral biovailability is made possible by the formation of a submicron emulsion by high pressure homogenization (See page 7, line 12 to 13 of applicants' specification).

The 337' patent does not add anything to the 195' patent that renders Claim 1 unpatentable. The 337' patent neither teaches nor suggests a submicron lipid emulsion. As a matter of fact it is unclear how it mixes the components to form the emulsion. In Column 6, lines 56-67 it is stated:

> "The method for preparing the lipid emulsion of the present invention will hereinafter be described in detail. Various known methods may be used. For instance, yolk lecithin and, if desired, phospholipids such as yolk phosphatidylethanolamine and auxiliary agents for emulsification such as oleic acid are dissolved in an appropriate organic solvent such as hexane and then the solvent is distilled off under reduced pressure to give a lipid film. To the resulting lipid film, there are added an oil component and water and the mixture is preliminarily emulsified by vigorously stirring through shaking. The resulting liquid is emulsified using the currently used emulsifier."

Furthermore, the emulsion of the 337' patent requires the presence of citric acid or a pharmaceutical salt thereof and at least one of a specific group of amino acids or a pharmaceutical acceptable salt thereof. In this regard, note Column 3, lines 47-49 where it is stated:

> "It is an essential requirement in the present invention to simultaneously use citric acid and at least one of the foregoing amino acids."

The 195' patent and 337' patent, either alone or in combination, fail to render Claim 1 obvious because they fail to teach or suggest the incorporation of the pyranone of

Formula I into a submicron lipid emulsion, (2) how to prepare such a submicron lipid emulsion, or (3) that such an emulsion would increase the oral biovailability of pyranone of Formula I. To prepare a submicron lipid emulsion containing lecithin, a high energy dispersion technique is necessary in order to reduce the particle size of such an emulsion. Apparently it is impossible to achieve a small particle size with lecithin by conventional emulsificaion methods without utilizing high energy dispersing equipment such as a high energy homogenizer.

Claims 2 to 4 further limit Claim 1 by requiring that the pyranone I be present in the composition in certain amounts. Therefore, these claims are patentably distinct over the 154' patent and the 337' patent for the reasons set forth in the rejection of Claim 1 and for the reasons that they contain additional limitations with respect to the amount of pyranone in the composition.

Claims 4 to 8 further limit Claim 1 by restricting the type and amount of lecithin in the composition. These claims are patentably distinct from the combination of 154' and 337' patents for the reasons set forth in the discussion of the rejection of Claim 1 as well as for the presence of additional limitations with respect to lecithin in the composition.

Claims 9 to 17 further limit Claim 1 by requiring the presence of specific oils and ratios of these oils in the oil component. The Examiner admits that the references do not teach or suggest the specific ratios or mixture of mono-, di-, and triglyceride recited in these claims, but nevertheless dismisses these limitations on the grounds that it would be obvious to optimize these ratios. There is no basis in law, fact or USPTO practice for the holding and the rejection should be withdrawn.

Claims 18 to 20 further limit Claim 1 by requiring that specific solvents be a part of the composition. Since these claims further limit Claim 1, they are patentably distinguished over the 154' and 337' patents for the reasons

set forth in the discussion of the rejection of Claim 1 as well as for the additional limitations in these claims.

Claim 21 limits Claim 1 to an oral or parenteral composition. It is patentably distinguished over the 154' and 337' patents for the reasons set forth in the discussion of the rejection of Claim 1.

New Claims 22 and 23 are directed to specific compositions of the instant invention. Claim 22 is supported by Examples 1,2 and 3 and Claim 23 by Examples 4 and 5. The 154' and 337' taken alone or in combination do not either teach or suggest the compositions defined in claims 22-23 for the reasons set forth in the discussion of the rejections of Claims 1-21 and for the presence of other limitations further distinguishing the compositions from the teachings of the 154' and 337' patents.

In view of the amendments and arguments set forth above, withdrawal of the rejection and expeditious passage of this application to issue is respectfully solicited.

Respectfully submitted,

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Encl: Exhibits A and B
Marked-Up Version of Amendments

136.9803

MARKED-UP VERSION OF AMENDMENTS

In the Specification:

Paragraph beginning at page 3, line 31, is amended as follows:

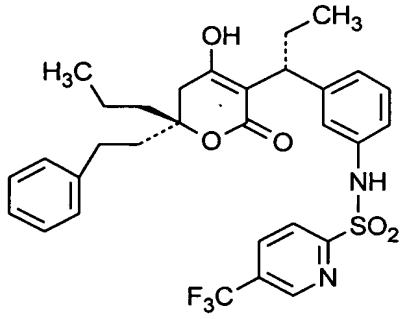
The present invention specifically provides a submicron lipid emulsion pharmaceutical composition which comprises:

In the Claims:

Claim 1 is amended as follows:

1. (Amended) A submicron lipid emulsion pharmaceutical composition comprising:

(a) a therapeutically effective amount of the compound of formula I



I

(b) an oil component selected from the group consisting of mono-, di-, tri-glyceride or a mixture thereof wherein the monoglyceride and diglyceride are mono- and di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon atom chain length, wherein triglyceride is a saturated fatty acid ester of glycerol having six to twelve carbon atom chain length,

(c) an emulsifying agent consisting of lecithin, and

(d) a liquid phase comprising one or more pharmaceutically acceptable solvents.

Claim 21 is amended as follows:

21. (Amended) ~~A~~ An oral or parenteral pharmaceutical composition of Claim 1 ~~which is administered orally or parenterally~~.